Review

Thoracic veins and the mechanisms of non-paroxysmal atrial fibrillation

Peng-Sheng Chen\textsuperscript{a,\*}, Tsu-Juey Wu\textsuperscript{b}, Chun Hwang\textsuperscript{c}, Shengmei Zhou\textsuperscript{a}, Yuji Okuyama\textsuperscript{a}, Akira Hamabe\textsuperscript{a}, Yasushi Miyauchi\textsuperscript{a}, Che-Ming Chang\textsuperscript{a}, Lan S. Chen\textsuperscript{d}, Michael C. Fishbein\textsuperscript{e}, Hrayr S. Karagueuzian\textsuperscript{a}

\textsuperscript{a}Division of Cardiology, Department of Medicine, Cedars-Sinai Medical Center, and UCLA School of Medicine, Los Angeles, CA, USA
\textsuperscript{b}Division of Cardiology, Department of Medicine, Taichung Veterans General Hospital and Institute of Clinical Medicine, National Yang-Ming University School of Medicine, Taipei, Taiwan
\textsuperscript{c}Utah Valley Regional Medical Center, Provo, UT, USA
\textsuperscript{d}Division of Neurology, Department of Pediatrics, Childrens Hospital Los Angeles and USC Keck School of Medicine, Los Angeles, CA, USA
\textsuperscript{e}Department of Pathology and Laboratory Medicine, UCLA School of Medicine, Los Angeles, CA, USA

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Abstract

Objective: The purpose of this article is to review the importance of thoracic veins in the maintenance of sustained (non-paroxysmal) atrial fibrillation (AF). Methods: Thoracic veins, including the pulmonary veins (PVs), vein of Marshall (VOM) and the superior vena cava (SVC), have muscle sleeves that connect to the atria. It is well known that electrical activities can be recorded within these venous structures. In some incidences, these thoracic veins may serve as the trigger and/or the substrate for paroxysmal AF. The importance of thoracic veins in chronic (sustained) AF is less well appreciated. Therefore, we review the literature to determine if thoracic veins are important in the maintenance of sustained AF. Results: Our recent study demonstrated that repetitive rapid electrical activities are present in the PVs and in the VOM during pacing-induced sustained AF in dogs. Because of these repetitive rapid activities, these thoracic veins have shorter activation cycle lengths than that of the left atrium, which, in turn, has shorter cycle lengths than that of the right atrium. Others have demonstrated that PV isolation in humans can result in a cure of sustained human AF in \textasciitilde 80\% of patients undergoing concomitant surgery. Conclusion: These findings suggest that repetitive rapid activities within the thoracic veins may be responsible for the maintenance of non-paroxysmal (sustained) AF. © 2002 Elsevier Science B.V. All rights reserved.

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1. Introduction

Recent studies show that paroxysmal atrial fibrillation (AF) may be initiated by repetitive rapid activities (RRAs) from the pulmonary veins (PVs) [1], the vein of Marshall (VOM) located in the posterior wall of the left atrium (LA) [2], or the superior vena cava (SVC) [3]. The importance of these venous structures in the maintenance of sustained (non-paroxysmal) AF is unclear. Our recent study [4] showed that both the VOM and PVs have shorter activation cycle lengths (ACLs) than the LA, which, in turn, has shorter ACLs than the RA during sustained AF. These findings suggest that thoracic veins are sources of RRAs in sustained AF. The purpose of this communication is to review the importance of the thoracic veins in the maintenance of non-paroxysmal (sustained) AF.

2. What are the thoracic veins?

Thoracic veins are the large veins in the thorax that
drain into the heart. In this communication, thoracic veins refer to the SVC, PVs, azygos vein and the vein of Marshall (VOM). While the human azygos vein does not have muscle sleeves, long muscle sleeves are found in canine azygos veins [5]. We will not discuss the inferior vena cava because it does not have muscle sleeves or electrical activity [5]. We will also not discuss the muscle sleeves around the coronary sinus. The muscle sleeves around the coronary sinus are potentially arrhythmogenic [6]. However, it is difficult to differentiate the activations within coronary sinus muscle sleeves and LA myocardium because these two structures may be closely connected and the connecting portion cannot be easily mapped [7].

3. Types of atrial fibrillation

There are at least two commonly used classifications of AF. One is to classify AF into either sustained AF or intermittent AF for the purpose of epidemiological studies. For example, Feinberg et al. [8] reported that the overall incidence of AF in the U.S. is 0.89%, affecting 2.23 million people. Among this large number of AF patients, roughly two-thirds have sustained AF and one-third have intermittent AF. Others [9] further classify clinical AF into three different categories based on both duration and response to treatment. Paroxysmal AF refers to episodes that generally stop spontaneously after no more than a few days. Persistent AF requires cardioversion to restore sinus rhythm. Permanent AF refers to AF that cannot be converted to sinus rhythm. For the purpose of this communication, we consider paroxysmal AF as intermittent AF. Both describe human AF episodes that terminate spontaneously. Many of these paroxysmal AF episodes have rapid firing foci within the thoracic veins [1–3]. We define sustained canine AF as canine AF that persists >48 h without spontaneous conversion. In our canine model, we have previously documented that some of the animals actually have permanent AF (cardioversion results in temporary success and immediate resumption of AF) [4]. When we cite other authors’ publications, we will use the same terms as used in those publications. ‘Chronic AF’, for example, is a commonly used term.

4. Anatomy and electrophysiology of the pulmonary veins

The embryological development of the PVs in the embryo is closely related to the development of the sinus venous segment of the heart [10–12]. In both mammals and the chick, the dorsal mesocardial connection (which connects the primitive atrium to the posterior thoracic wall) forms a fixed point through which the PVs gain access to the atria. In human embryos, there is atrial musculature in thoracic veins and the extension of cardiac muscle into the thoracic veins is far greater than that found in children and adults [5]. While adults have less cardiac muscle extension than the embryo, a significant amount of muscles is still present [13–15]. The cardiac muscle in PVs connects directly to the LA. Nathan et al. [13] showed that the muscle fibers in PVs are usually oriented perpendicularly to the blood flow. This orientation would predict anisotropic electrical propagation patterns in the PVs, with more rapid excitation around the PVs than along the PVs.

In 1876, Brunton and Fayer [16] demonstrated independent PV contractions in rabbits and cats. After artificial respiration of the anesthetized animals was discontinued, the PVs pulsed at a rate of 119 beats/min, but the contraction of the PVs was asynchronous with the atria. They also noted that, while both atria subsequently ceased to beat, the PVs in both lungs continued to pulse. These seminal observations have two important implications. The first is that the PVs have contractile muscle fibers. The second is that the PV is capable of generating electrical activity independent of the atria. Findings by other investigators are compatible with these results. Masani et al. [17] showed that node-like cells are present in the myocardial layer of the PV of rats. In rabbit sinocaval preparation, Ito et al. [18] demonstrated spontaneous diastolic depolarization that could lead to automatic activity. Cheung [19] reported that isolated PVs were capable of independent pace-making activity, and the electrical activity in the PVs was presumed to be a result of cardiac musculature because the smooth muscle present was noted to be electrically quiescent. Cheung [20] also demonstrated that ouabain infusion or norepinephrine infusion could trigger the onset of RRAs from the distal PV but not in the adjacent atrial cells. More recently, Chen et al. [21] performed transmembrane potential recording of canine PVs using standard glass microelectrodes. They reported several types of electrical activities within the PVs, including fast response action potentials driven by electrical stimulation, and spontaneous fast or slow response action potentials with or without early afterdepolarizations. The incidences of action potentials with an early afterdepolarization and of spontaneous tachycardia were much greater in dogs with chronic pacing than in normal dogs. The authors concluded that PVs have an arrhythmogenic ability through spontaneous activities or high-frequency irregular rhythms. The higher incidence of spontaneously occurring high-frequency irregular rhythms in dogs with chronic rapid pacing may account for the increased risk of AF in these dogs.

5. Anatomy and electrophysiology of the ligament of Marshall

In 1850, Marshall [22] described the presence of a ‘‘vestigial fold of the pericardium’’ in humans, which had until then ‘‘escaped attention’’. A developmental vestige of the left primitive veins, this vestigial fold is located in the
back of the left auricle, running from the coronary sinus upward to the region near the orifice of the left superior PV. In some cases, Marshall observed that this vestigial structure is connected to the small oblique auricular vein that drains into the coronary sinus. The LOM again escaped attention for another 100 years until Scherlag [23] discovered the potential electrophysiological importance of this vestigial fold. In that study, Scherlag et al. reported that there are electrically active muscle sleeves (Marshall bundles) within the LOM. These muscle sleeves serve as the origin of the second potential in the double potential recorded in that area. In addition to having muscle sleeves, the LOM also contains the VOM, whose orifice serves as the landmark that separates the coronary sinus from the great cardiac vein [7]. The muscle sleeves around the coronary sinus continue into the LOM, forming the inferior interatrial pathway. The great cardiac vein, on the other hand, is not surrounded by muscle sleeves.

To demonstrate the importance of LOM in arrhythmogenesis, we performed further studies on this fascinating structure. Doshi et al. [24] showed that the LOM is a source of rapid focal discharge in vitro using isolated LA from dogs with pacing-induced sustained AF. Hwang et al. [2,25] took this concept to humans and showed that the LOM is a source of paroxysmal AF in humans. Kim et al. [26] performed histopathological analyses of the human LOM and showed that there are complicated connections between the muscle bundle (Marshall bundle) within the LOM and the coronary sinus. The other end of the Marshall bundle might connect directly to the LA free wall. Naik et al. [27] demonstrated electrical potentials within the persistent left superior vena cava in a patient with atrial tachyarrhythmia. Those electrical potentials resemble the double potentials recorded in the VOM [2,25], further supporting the concept that VOM is a developmental remnant of the left superior vena cava. We [28–30] and others [31] reported that a direct connection between the Marshall bundle and the LA free wall is indeed present in humans and in dogs. Furthermore, ablation of the LOM may change the morphology and lengthen the duration of the P wave on canine surface electrocardiograms [30].

We analyzed the ACLs at the LOM in a canine model of sustained AF [4]. The results showed that both the VOM and PVs have shorter ACLs than the LA, which, in turn, has shorter ACLs than the RA during sustained AF. These preliminary results show that, like the PVs, the LOM is also a source of RRAs in sustained AF.

6. Superior vena cava: another possible source of RRAs in AF

The anatomical junction of the SVC and the RA is at the base of the RA appendage. In human patients, Spach et al. [5] registered cardiac excitation 2–5 cm above that junction. However, no cardiac excitation extends into the azygos vein or the inferior vena cava. In dogs, cardiac excitation and cardiac muscle extend even further into the SVC (5–6 cm). The excitation even extends into the azygos vein from its origin to as far as the vertebral body. The importance of the SVC in AF was unknown until recently, when Tsai et al. [3] reported that 6% of their patients with paroxysmal AF had fast ectopic beats originating from the SVC. Furthermore, paroxysmal AF in these patients could be cured with radiofrequency ablation delivered within the SVC. Thus, the SVC should also be considered as a possible source of RRAs in AF.

7. Mechanisms of AF: the remodeling hypothesis

According to the remodeling hypothesis, the RRAs from PVs serve as a “trigger” for AF. The activation starting from the trigger propagates to the atria, initiating reentry within the atrial musculature, resulting in AF [9]. In normal atria, the reentry may self-terminate, resulting in non-sustained AF episodes. An appropriate “substrate” is necessary for reentry to continue. Studies [32,33] have shown that rapid pacing indeed alters the “substrate” of AF by electrophysiological and morphological remodeling. The changes include significant alteration of ionic channel activity and increased spatial heterogeneity of ion channel function [34]. Due to these remodeling changes, the substrate of AF is enhanced, and reentry is more likely to sustain. In other words, AF begets AF [32]. If this hypothesis is correct, prevention of AF relies, in part, on early cardioversion and aggressive management of non-sustained AF episodes [9]. Future development of drugs that reverse electrical remodeling is another possible approach. Until such drugs are developed, maze or compartmental surgeries are needed to cure permanent AF [35].

8. Mechanisms of AF: the thoracic vein hypothesis

An alternative hypothesis of AF is that the RRAs from the thoracic veins are both the “trigger” and the “substrate” for the maintenance of AF. In this scenario, the electrical and structural remodeling of the atria is not important in the maintenance of AF. A prediction of this hypothesis is that AF can be cured if we eliminate the rapid activity from thoracic veins. Prinzmetal et al. [36] proposed that RRAs induced by aconitine could create atrial tachyarrhythmias, including AF. Moe and Abildskov [37] demonstrated that aconitine injection into the atrial appendage could induce AF. Application of a clamp at the base of the auricle resulted in immediate resumption of sinus rhythm in the body of the atrium while the tachycardia persisted in the auricle, whether or not the vagus was stimulated. Therefore, without the aconitine focus, AF cannot sustain. Recent clinical studies indicate that, in paroxysmal AF, RRAs appear to be both the substrate and
the trigger of AF in some patients [38]. Ablation of the RRAs within the thoracic veins may result in both acute termination of AF and long-term prevention of AF recurrence [1–3,5,39,40], supporting the claim that the RRAs within the thoracic veins are both the trigger and the substrate of paroxysmal AF.

9. Thoracic veins and sustained AF: experimental evidence

Is this alternative hypothesis applicable to sustained AF in humans? It is known that, during sustained AF in humans [41], the LA activates faster than the RA. Small areas of particularly short ACLs can be identified in the PV orifice region [41]. Even more promising is that a combination of mitral valve surgery, cryoablation of the PV orifice, and resection of the LA appendage cured 10 of 12 patients with chronic AF and mitral valve disease [42]. Another report indicated that simple isolation of the PV orifice concomitant with mitral valve replacement was sufficient to cure chronic AF in a 61-year-old woman [43]. More recently, Williams et al. [44] performed endocardial PV isolation on 48 patients with AF undergoing concurrent operation using temperature-controlled radiofrequency energy delivered through a hand-held flexible probe. The duration of AF before surgery was 4.8±6.4 years. The results of 42 patients were included in the final analyses. At a mean follow-up of 138±96 days after surgery, 34 of 42 patients (81%) were in sinus rhythm. While these data provide no definitive proof, they are consistent with the thoracic vein hypothesis of sustained AF.

Many investigators have demonstrated that, during sustained AF in dogs [33,45], the LA activates at shorter ACL than the RA. Small areas of particularly short ACL can be identified in the PV orifice region in the posterior LA [33]. If the PVs and VOM are important in sustaining AF, it follows that these structures should be activating at shorter ACL than the LA and RA. Using computerized mapping techniques we [4] studied the activation rate in a canine model of pacing-induced sustained AF. We induced sustained AF (>48 h) in six dogs by rapid pacing for 139±84 days. We then performed computerized atrial epicardial mappings and determined the ACL in the LOM and the PVs. During AF, the mean ACL in the RA free wall (126±17 ms) was significantly longer than that in the LA free wall (96±5 ms, P=0.006). In addition, the mean ACL in the LA free wall was significantly longer than that in the LOM (84±5 ms, P<0.001), the left inferior PV (81±4 ms, P=0.001) and the left superior PV (85±7 ms, P=0.003). Similarly, the dominant frequency was highest in the LOM and the PVs (range 11.2 to 13.3 Hz), followed by the left and the right atria (P<0.001). Fig. 1 shows examples of actual recordings, dominant frequency analyses and the method used to determine ACL. In all dogs studied, rapid and complicated electrograms were consistently observed at the LOM and the PVs. However, because we used closely spaced bipolar electrodes, we can still determine the ACL based on objective criteria. During AF, the ACL in PV and VOM were shorter than in the LA, which, in turn, had shorter ACL than RA. Both wandering wavelets and organized reentry were present in the atria. There were more wavefronts in the LA than in the RA (P<0.001). These results show that, in chronic pacing-induced sustained AF, the LOM and the PVs are the sources of RRAs. The mechanism by which the LA has shorter ACLs than the RA may be due to the fact that the LA is closer to the sources of RRAs.

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10. Limitations

One limitation is that only a few studies have documented the importance of LOM in AF [2,48]. Therefore, more studies of LOM are needed to document its importance in the generation and maintenance of AF. A second limitation is that, in the animal model reported by Wu et al. [4], there was no detailed mapping to determine the direction of wavefronts in the PVs. It is possible that the wavefronts originated in the LA undergo fibrillatory conduction and invade the PV, resulting in fractionated activities. However, we have since performed detailed mapping studies and showed that these RRAs in fact originated from the PV and propagated towards the LA [47]. A third limitation is that there are no animal experiments showing that thoracic vein ablation can terminate sustained AF. However, Williams et al. [44] have shown that PV isolation can result in a high cure rate of sustained AF in humans. While there is no conclusive evidence in support of the thoracic vein hypothesis, we believe that the hypothesis is plausible and deserves further investigation.
Fig. 1. Simultaneous multisite recordings during sustained AF. (A) Mapping areas, including the epicardial surfaces of the LA (plaques #1 and #2) and the RA (plaques #3 and #4) free walls, the interatrial septum, the LOM, and the PVs. (B) Actual activations registered from different regions. (C) An example of activation time determination. The computer selected a time as the local activation if $\frac{dV}{dt}$ exceeded 20% of the maximal $\frac{dV}{dt}$ in that channel and if an interval of 50 ms has passed since a previous activation. The activations selected by the computer were marked by vertical lines. Manual editing was then performed to select other activations (vertical arrows) with $\frac{dV}{dt}$, > 20% of the maximum. The deflections within 50 ms from a computer-selected activation were not selected manually (asterisks). (D) FFTs for selected channels in (B). Arrows and numbers indicate the dominant peak and the dominant frequency (Hz), respectively. AVR, atrioventricular ring; BB, Bachmann’s bundle; IVC, inferior vena cava; LIPV, left inferior PV; LSPV, left superior PV; Plt, recording electrode plaque; RIPV, right inferior PV; RSPV, right superior PV; SVC, superior vena cava. (From Ref. [4], with permission.)

11. Summary

In this communication we propose the thoracic vein hypothesis of non-paroxysmal (sustained) AF. The hypothesis states that the thoracic veins serve as sources of RRAs during sustained AF. Surgical or pharmacological elimination of RRAs within the thoracic veins may lead to the cure of sustained AF.

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